REMARKS

It is respectfully requested that this amendment be entered. The amendment does not raise new issues and does not require any additional searches.

Claims 1-44 have been cancelled and claims 45-82 have been added.

Claim 45 defines a stable pharmaceutical composition comprising a therapeutically effective amount of benzoquinolizine-2-carboxylic acid antimicrobial drug or a pharmaceutically acceptable salt, solvate or derivative thereof selected from group consisting of:

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate; and

RS-(+-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid; and

a pharmaceutically acceptable solubilizing agent selected from the group consisting of basic amino acids, a cyclodextrin and a cyclodextrin polymer or a mixture thereof;

wherein the concentration of the drug that is maintained in solution with the solubilizing agent is above the practical limit of solubility of the drug as compared to the

solubility of the drug when the drug is not in solution with the solubilizing agent, wherein the solution is a substantially isotonic aqueous solution at a physiologically compatible pH.

Except for the inclusion of derivatives of cyclodextrin polymers in the list of solubilizing agents, claim 68 is the same as claim 45.

Claims 45 and 68 correspond substantially to claim 1 except that in claims 45 and 68 specific benzoquinolizine-2-carboxylic acid drugs are defined.

The term stable used in this claim is described in paragraph [0012] of the application as originally filed. The term stable is described a stable to light under normal conditions for use and stable to temperature while having a pH compatible with direct administration.

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt; is defined in original claim 10.

Compounds S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate; and

RS-(+-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid were included in original claim 9.

For the examiner's convenience, the following is a chart of the concordance between the current set of claims and claims that were examined previously.

Prior claim	Current claim
Claims 1, and 9-12	Claims 45 and 68
Claim 4-6	Claims 46-48
Claim 10	Claim 59
Claim 12	Claim 60
Claim 14	Claim 49
Claim 15	Claim 50
Claim 17	Claim 51
Claim 18	Claim 52
Claim 19	Claim 53
Claim 20	Claim 54
Claim 21	Claim 55
Claim 2	Claim 56
Claim 3	Claim 57
Claim 23	Claim 58
Claim 36	Claim 69 (see discussion below)
Claim 37	Claim 70
Claim 38	Claim 71
Claim 39	Claims 77 and 78
Claim 42	Claim 73
Claim 43	Claim 74
Claim 44	Claim 76
Claim 33	Claim 81 (see discussion below)
Claim 34	Claim 82

Claim 69 defines a method for treating a bacterial infection by administering a composition according to claim 45.

Claim 81 defines a method for preparing a composition wherein the concentration of the solubilizing agent is sufficient to maintain the drug in solution at a drug concentration

that is above the practical limit of solubility of the drug as compared to the solubility of the drug when the drug is not in solution with the solubilizing agent, wherein the solution is a substantially isotonic aqueous solution at a physiologically compatible pH.

According to the official action, claims 1-10, 12, 14, 15, 22-27, 30-39, 42, 43 and 44 are rejected under 35 USC 102(e) in view of de Souza et al. (US patent 6,514,986). This is respectfully traversed.

Claim 45 of this application provides that the composition contain an effective amount of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate; and

RS-(+-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid; and in addition to the drug a pharmaceutically acceptable solubilizing agent selected from the group consisting of basic amino acids, a cyclodextrin and, a cyclodextrin polymer; or a mixture thereof and that the concentration of the drug that is maintained in solution with the solubilizing agent is above the practical limit of solubility of the drug as compared to the solubility of the drug when the drug is not in solution with the solubilizing agent, wherein the solution is a substantially isotonic aqueous solution at a physiologically compatible pH.

As stated in the previous response "Anticipation requires that each and every element of the claimed invention be disclosed in a single prior art reference. *In re Paulsen*,

30 F.3d 1475, 31 USPQ 1671 (Fed. Cir. 1994). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Res. Found. v. Genentech, Inc.,* 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991)."

The '986 patent does not disclose each and every element of claims 1-10, 12, 14, 15, 22-27, 30-39, 42, 43 and 44 and therefore, cannot anticipate these claims. The '968 patent does not describe a composition which includes a solubilizing agent as defined in claims 45 and 68 in addition to the drug.

According to examples 1-5 of the '968 S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt is prepared by mixing the S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid with an organic solvent. The invention claimed in this application is not preparation of amino acid salts, inorganic base and alkali salts and organic base salts of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid. It relates to compositions, use of these compositions and preparation of these compositions using S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid or a amino acid salt or hydrate thereof and **a solubilizing agent**. This is not disclosed in the '986 patent.

According to example 1 of the '986 patent the crystalline S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid arginine salt is prepared by adding a solution of L-(+)-arginine in distilled water dropwise to the stirred solution/suspension of finely powdered S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid in acetone. The solution is stirred for 30 minutes and concentrated on a water bath in vacuum (175 mbar) at 80° C up to dryness. Hexane (1 liter) was added, the reaction mixture was stirred for 4 hr, the solid thus separated was filtered and dried.

In example 2 of the '986 patent the process of example 1 is carried out using acetonitrile instead of acetone.

In example 3 of the'986 patent the process of example 1 is carried out using methanol instead of acetone.

In example 4 of the'986 patent the process of example 1 is carried out using ethanol instead of acetone.

In example 5 of the'986 patent the process of example 1 is carried out using isopropanol instead of acetone.

These examples, as well as claims 13-16, describe preparation of crystalline and amorphous S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid arginine salts and do not describe preparation of a composition that contains one or more of these compounds and an additional component which is a solubilizing agent.

The examiner's attention is drawn to original paragraph [0033] of this application in which it is disclosed that S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid arginine salt can be prepared by the processes described in US patent 6,514,986. It is the combination of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid arginine salt, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate or RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid with a solubilizing agent that is not disclosed in the the '986 patent and is novel. The examiner is respectfully requested to review test example 1 of this application which describes a solubility study with arginine. Test example

1 describes a study that was conducted to examine the solubility of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid and its arginine salt in an aqueous system containing different concentrations of arginine.

Aqueous solutions of L-arginine at concentrations of 5, 10, 15, 25, 50, 100 and 200 mg/ml were prepared. 3 ml of each of these solutions was added to an accurately weighed amount of S-(-)-9-fluoro-6,7-dihydro-8-(4- hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[l,j]quinolizine-2-carboxylic acid (Subs. "A") and separately to S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[l,j]quinolizine-2-carboxylic acid arginine salt (Subs. "B"). The flasks were kept ca. 16 hours on a mechanical shaker, maintained at 27^0 C. and 140 rpm. The solutions were filtered through 0.2 micron syringe filter. The filtrates were diluted appropriately and injected on HPLC.

From this it is clear that the invention claimed in this application is novel and not anticipated by the disclosure of the '986 patent.

Firstly, S-(-)-9-fluoro-6,7-dihydro-8-(4-- hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[l,j]quinolizine-2-carboxylic acid (Subs. "A") and S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[l,j]quinolizine-2-carboxylic acid arginine salt are being solubilized in L-arginine. The compound and the L-arginine salt thereof are mixed, maintained at ambient temperature on a mechanical shaker for about 16 hours. No organic solvent is added as described in examples 1-5 of the '986 patent.

Secondly, the solubility data shows that the arginine salt form of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid is not formed when S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid is mixed with L-arginine according to the procedure of text example 1 of this application.

This application describes the preparation of compositions for injection. According to example 1 of the application, the solution for injection is formed by mixing the S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt with L-arginine in water. According to example 2, the solution for injection is formed by mixing the S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid with L-arginine in water. Examples 3-18 also describe the preparation of compositions for injection. In test example 1, the solubility of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt and S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid in various concentrations of arginine is determined. From this it is also clear that the invention is a composition that includes a solubilizing agent that is separate and apart from the drug. When L-arginine is used as a solubilizing agent with the carboxylic acid, the arginine salt of the carboxylic acid is not formed.

Contrary to what the examiner states, the disclosure at col. 8, lines 29-33 of the '986 does not disclose the claimed invention as there is no disclosure of the use of a solubilizing agent.

According to column 2, lines 29-34 of the '986 patent, amino acid salts, inorganic base and alkali salts and organic base salts of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j] quinolizine-2-carboxylic acid were prepared. This does not disclose the use of a solubilizing agent that results in a concentration of the drug that is above the practical limit of solubility of the drug as compared to the solubility of the drug when it is not in solution with a solubilizing agent.

The disclosure in the abstract and in col. 8, lines 23, 35-38 and 47, col., 6, lines 44-50; column 4, lines 39-40, and claim 17 describe S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid arginine salt. There is no disclosure of this compound S-(-)-9-fluoro-6,7-dihydro-8-(4-

hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[I,j]quinolizine-2-carboxylic acid arginine salt being mixed with and dissolved in a solution with a solubilizing agent.

The disclosure in col. 1, lines 50-53 describes that S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid has a pKa value of 6.80 suggesting a weak acid character and thus an ability to form a salt with an appropriate base. This does not disclose the claimed invention. As described above, the arginine salt of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid is prepared using an organic solvent. According to this invention the arginine salt of S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid, S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid 0.2 hydrate or RS-(±)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo[i,j]quinolizine-2-carboxylic acid are mixed with a solubilizing agent. This differs from preparing a salt form of a compound.

As explained above, there is no disclosure in the '986 patent of a stable pharmaceutical composition comprising a therapeutically effective amount of benzoquinolizine-2-carboxylic acid antimicrobial drug or a pharmaceutically acceptable salt, solvate or derivative thereof selected from group consisting of:

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid arginine salt;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid;

S-(-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid 0.2 hydrate; and

RS-(+-)-9-fluoro-6,7-dihydro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-1H,5H-benzo [i,j]quinolizine-2-carboxylic acid; and

a pharmaceutically acceptable solubilizing agent selected from the group consisting of basic amino acids, cyclodextrin, a cyclodextrin polymer or a derivative thereof; or a mixture thereof;

wherein the concentration of the drug that is maintained in solution with the solubilizing agent is above the practical limit of solubility of the drug as compared to the solubility of the drug when the drug is not in solution with the solubilizing agent, wherein the solution is a substantially isotonic aqueous solution at a physiologically compatible pH.

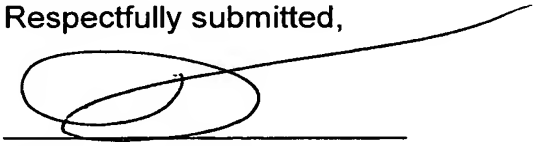
There is no disclosure in the '986 patent of the use of this composition for treating a bacterial infection and preparation of this composition.

As the '986 patent does disclose each and every element of the claims, this patent cannot and does not anticipate claims 1-10, 12, 14, 15, 22-27, 30-39, 42, 43 and 44 nor the claims presented in this response.

It is respectfully requested that the rejection be withdrawn.

It is submitted that the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,



JANET I. CORD
LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG.NO.33778(212)708-1935